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Review Article

3D'S FOR NEUROPATHIC PAIN - DIAGNOSIS, DRUGS AND DEVICES

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ABSTRACT

Today huge population worldwide is affected with the chronic debilitating neuropathic pain. A high level of dexterity is required for the diagnosis of neuropathic pain as it can develop gradually with time. Diagnosing and treating neuropathic pain is still a challenge to clinicians but if it is suspected, then various diagnostic screening tools such as neuropathic pain scale, Leeds assessment of neuropathic symptoms and signs, The neuropathic pain questionnaire, Douleur Neuropathique en four questions may be valuable. These verbal questionnaires afford valuable information to the clinician regarding the pain as neuropathic pain portrays some exclusive symptoms usually described as burning, painful, cold or electric shocks which may be coupled with tingling, numbness or itching. This review decisively examines the role of various mediators involved in transmission of neuropathic pain and highlights the potential therapeutic opportunities to arbitrate diagnosis and treatments of neuropathic pain.

Keywords: Nitric oxide, Bradykinins, Antidepressants, Antiepileptics.

INTRODUCTION

Neuropathic pain is lately redefined as pain arising as a direct consequence of a lesion or dysfunction of nervous system.[1] The control of neuropathic pain symptoms is always partial despite taking prescribed medications for pain and adverse effects associated to treatment frequently make it unbearable.[2] There are several etiologic causes of neuropathic pain which include infectious agents, trauma, metabolic diseases, neurodegenerative diseases and many others.[3] Commonly observed symptoms in neuropathic pain include paresthesias , dysesthesias , hyperesthesia , hyperpathia ,and allodynia .The neuropathic pain can be stimulus evoked, spontaneous, or can be a amalgamation of both.[4] The symptoms in neuropathic pain are highly debilitating and deteriorate the quality of life of patient. The pathogenesis of neuropathic pain involves the interaction between the immune system and the nervous system and many mediators are also implicated in neuropathic pain which alters local homeostasis and impairs neuronal function.[5] The treatment of neuropathic pain is initiated by drugs but if they are incapable to control the symptoms then many other novel techniques can be used such as spinal cord stimulation, deep brain stimulation, peripheral nerve stimulation, percutaneous nerve stimulation, percutaneous neuromodulation therapy, electroalgesia, transcutaneous electrical nerve stimulation, Transcutaneous Acupoint Electrical Stimulation, Interferential Current Therapy, Piezo-Electric Current Therapy, H wave therapy.[6] This review article states the current diagnostic, pharmacologic treatments and devices used for neuropathic pain.

3 D's for neuropathic pain

1) Diagnosis

Neuropathic pain diagnosis starts with collecting detailed medical history of patient and examination of symptoms accompanied with scrupulous neurological and physical examination.[7] Reviewing medical history provides insight into onset, site, distribution and possible cause of pain. Nature of pain (eg- allodynia, paresthesias, and hyperesthesia) should be diligently recorded. Since the diagnosis

of neuropathic pain relies largely on the manifestation of sensory abnormalities in the affected area. Several tools are devised for comprehensive diagnosis of neuropathic pain namely; Neuropathic pain scale (NPS), Leeds assessment of neuropathic symptoms and signs (LANSS), The neuropathic pain questionnaire (NPQ), Douleur Neuropathique en 4 questions (DNA), Pain DETECT and ID- pain.

- NPS (neuropathic pain scale) – It contains 10 items provides a reproducible assessment of the type of symptoms experienced by the patient which help the clinician to design the treatment regimen for the patient.[8]
- LANSS (Leeds assessment of neuropathic symptoms and signs) - contains 5 symptom items and two clinical examinations items. A score of 12 or above out of 24 suggests neuropathic pain. The LANSS has been tested and validated for its sensitivity and specificity ranging from 82% - 92% and 80% - 94% respectively.
- NPQ (neuropathic pain questionnaire) – It is composed of 12 items that include 10 related sensations and 2 related to affects. The precise form of NPQ maintained similar discriminative properties with only 3 items namely tingling, numbness, and increase in pain upon touching.
- DNA (Douleur Neuropathique en 4 questions) – It includes of total 10 items out of which 7 are related to symptoms and 3 with clinical assessment. It is easy to score and total score of 4 or more out of 10 indicates neuropathic pain
- Pain DETECT – It is a self reporting questionnaire with 9 items. It does not require any clinical examination. It has been translated to 22 languages and it is also available in English.
- ID- Pain – It includes of 5 sensory items and 1 item relating to presence of pain in joints. It does not require any clinical assessment.[9]

Inflammatory mediators involved in neuropathic pain

- Bradykinin- It is among the most potent sensitizing agents. It has been known that upon injecting bradykinin into human skin it produces a dose related pain and heat hyperalgesia which suggests that bradykinin is able to excite and sensitise nociceptors to high temperature.[10] Release of bradykinin further causes release of other neurotransmitters and mediators from immune cells such as calcitonin, substance P and acetylcholine and NGF, interleukins, tumour necrosis factor ,prostaglandins, leukotrienes respectively.[11, 12]
- Prostaglandins-(PG) are derivatives of arachidonic acid, which is released from membrane phospholipids. PGE_2 and PGI_2 are more powerful sensitizers than PGF_{2a}, PGD_2 or TxA_2[13] Most NSAIDS inhibit the production of prostaglandins through cyclooxygenase pathway. Blocking Cyclooxygenase reduces the excitation of neurones.[14] Other than arachidonic acid prostaglandins can also be produced by lipoxygenases and cytochrome P450 epoxygenase.[15] Link between COX-2 induced prostaglandin release and increased nociception in neuropathic pain has been shown by some studies.[16- 18]
- Serotonin- Elevated levels of serotonin, or 5-hydroxytryptamine (5-HT) is found in inflamed tissues, and is released mainly from mast cells and platelets[19]. Serotonin is capable of directly exciting neurones through 5-HT_3 receptor and Gq coupled 5-HT_{2A} receptors present in neurones.[20, 21] Inflammatory pain was shown to be relieved by using 5-HT_{2A} antagonist.[22]
- Neurotrophins-It includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin 3-5 which activate the tyrosine kinase-couples receptors. Neurotrophins are capable of imparting both short term and long term effects, phosphorylation of ion channels is responsible for short term effects and long-term changes are caused by changes in gene expression.[23, 24] Injecting NGF causes a brisk and long lasting hyperalgesia.[25]
- Nitric oxide - (NO) is produced in body by the nitric oxide synthases, and there exist three isoforms of nitric oxide, endothelial (eNOS), neuronal (nNOS) and inducible (iNOS). Nitric oxide is a short-lived inflammatory mediator and therefore generally produces local effects, but it can pass quickly through cell membranes and therefore often effects are seen in neighbouring cells of nitric oxide

producing cell. Noxious irritants or NO itself is capable of producing NO synthesizing enzymes.[26-28]. Inflammatory hyperalgesia is reduced by local inhibition of NO synthesis.[29]

- Cytokines – These are tiny proteins expressed on the cell surface in precursor form, which can be cleaved to allow quick release, as a result of which they can diffuse to act on another cell. Originally name, interleukin (IL), derives from the fact many of them are produced by leukocytes and act on leukocytes, although they can also be produced by most cell types. Cytokines come in two opposite phenotypes; the pro-inflammatory (IL-1β, TNF, IL-6, IL-15, IL-17, IL-18, and IFN-γ) and anti-inflammatory (IL-4, IL-10 and TGF-β). Furthermore, it is also apparent IL-1β, TNF and IL-6 induce the production of each other through positive feedback mechanism and act synergistically to augment the signals of inflammation[30], which can lead to chronic inflammation if left untreated. Pro-inflammatory cytokines often cause algesia indirectly, through release of further mediators, such as NO and PGE_2, which sensitise nociceptors.[31]
- Calcium Channels -Transformation of calcium influx into the cytoplasm by voltage gated calcium channels affects neuronal excitability and promotes exocytosis of neuropeptides such as substance P and calcitonin gene related peptide from nociceptive neurones.[32, 33] Till now, ten genes encoding voltage gated calcium channels have been identified and have been grouped into three families: Ca_v1. family ($Ca_v1.1$-1.4 corresponds to L-type current), the Ca_v2 family includes $Ca_v2.1$ (P/Q current), $Ca_v2.2$ (N-type current), $Ca_v2.3$ (R-type current) and the Ca_v3. ($Ca_v3.1$-3.3 corresponds to the T-type current).[34]
- Sodium channels -They are thought to play a key role in numerous chronic painful neuropathies resulting from injury to the peripheral nerves.The voltage gated Na^+ channels is composed of the family of nine structurally related α subunits (Nav1.1 to $Na_v1.9$) which show distinct expression patterns and are associated with one or more accessory β subunits (β1 to β3).[35-37] The sodium channels in injured nerves exhibit different depolarization characteristics from undamaged nerves.[38, 39] The transformed sodium channels have modified properties that contribute to hyperexcitability in the DRG, increased pain transmission, and sensitization.[40]

2) Drugs employed in treatment of neuropathic pain

Treatment of neuropathic pain is still a challenge to clinicians as the neuropathic pain symptoms are not entirely controlled even after drug therapy. Except the prototype symptoms of NP there also exist several other emotional and psychological symptoms. During initiation of treatment the patient must be educated regarding neuropathic pain and significant side effects associated with the drug therapy this helps increase patient compliance. Neuropathic pain is generally unresponsive to NSAID therapy; however certain other pharmacological classes of drugs are found effective in controlling symptoms of NP these include antidepressants, antiepileptics, analgesics (opioids and NSAID'S) and local anaesthetics. [41]

Antiepileptics

There is a long history of using antiepileptic drugs for treatment of neuropathic pain, but they all have potential to cause adverse effects such as drowsiness, dizziness and ataxia. Gabapentin and pregabalin have been most extensively used in patients with diabetic neuropathy and post-herpetic neuralgia. These two drugs act by modifying the voltage-gated calcium channels of primary afferents thus interfere with the release of substance P, norepinephrine and the excitatory amino acid neurotransmitter glutamate.[42-44] Antiepileptics are found effective on pain as well as on paresthesias and dysesthesias.[45] Newer drugs like Lamotrigine and topiramate have slightly different mechanisms of action which increases their spectrum of efficacy as compared to other standard antiepileptics. Lamotrigine acts by blocking sodium channels and reducing glutamate release. Topiramate also acts by blocking sodium channels and may also act on AMPA (amino-3-hydroxy-5-methyl- 4-isoxalon)/ kainate receptors.[46]

Antidepressants
This has been widely recognized that antidepressants induce specific analgesic activity, which is mainly due to central inhibition of serotonin and noradrenaline reuptake which results in augmentation of the downward monoaminergic inhibitory mechanisms.[47] Tricyclic antidepressants have been extensively used to treat almost all types of neuropathic pain.[48] The selective norepinephrine and serotonin reuptake inhibitors duloxetine and venlafaxine are found valuable in controlling painful polyneuropathic pain.[3, 48–49]

Local anaesthetics
Topical anaesthetics are safe to use and relieve pain that's why recommended in first line treatment of localised neuropathic pain such as postherpetic neuralgia.[50, 51]
Lidocaine alleviates pain mainly by blocking sodium channels on peripheral afferent fibres without causing any numbness of the treated skin. The topical application lidocaine provides relief without a relevant systemic absorption thus it is widely used for localised peripheral neuropathic pain. Side effects of local application of lidocaine include erythema or rash.[52]

Opioid and Tramadol
Opioid analgesics act as agonists postsynaptic and presynaptic opioid receptor. Tramadol also inhibits neuronal reuptake of serotonin and norepinephrine. The analgesic effect of opioids is comparable to tricyclic antidepressants. Long term opioid therapy is always associated with the risk of physical dependency and misuse or abuse which generally restricts their use.[53-56] Opioids are used for treating pain which resistant to other drugs. Opioid therapy is initiated with lowest effective dose and up escalated gradually.[57]

Analgesics
NSAID'S are usually unsuccessful in neuropathic pain treatment. NSAID'S therapy is accompanied with side effects so their dose is gradually increased to minimise the adverse effects and obtain better control over pain.[58]

Botulinum Toxin
Botulinum toxin type A (BTX-A) is a new ray of hope for neuropathic pain sufferers when injected intradermally it relieves pain possibly by reducing neurogenic inflammation. The first evidence regarding the analgesic activity of BTX-A in focal neuropathy was shown in year 2008.[59] Upon single intradermal injection of BTX-A, subjects reported reduction in pain severity during whole course of study (24 weeks), as well as decrease in brush-induced allodynia at 4 and 12 weeks after treatment was accounted but still there is a lot to be explored.[60,61]

Herbal drugs
Ginkgo biloba
Ginkgo is obtained from the dried leaves of Ginkgo biloba Linn., belonging to the family Ginkgoaceae. According to a study Ginkgo biloba has decreased thermal hyperalgesia in a carrageenan induced inflammatory pain model.The positive effect of Ginkgo biloba extract in NP is primarily due to a combination of an antioxidant, anti-inflammatory and antagonistic action against platelet activating factor and also has a defensive effect against neurotoxicity induced by N-methyl-D-aspartate (NMDA).[62, 63]

Panax ginseng
The biological source of Ginseng is the dried root of various species of Panax, like P.ginseng (Korean ginseng), P.japonica (Japanese ginseng), P. Notoginseng (Chinese ginseng) and P.quinquefolium (American ginseng), belonging to the family Araliaceae. A polyacetylenic compound, (9R, 10S)-epoxyheptadecan-4,6-diyn-3-one (EHD), isolated from ginseng extract. The mechanism by which ginseng provides relief in NP is through inhibition of voltage-gated Na+ channels in primary sensory neurons which have been widely implicated in the pathogenesis of NP sensitivity.[64]

Emblica officinalis
The valuable constituents in E.officinalis are antioxidants such as Vitamin-C, flavanoids and tannins; they have free radical scavenging activity. Quercetin, a bioflavonoid is reported to alleviate neuropathic pain symptoms by inhibition of lipid peroxidation and restitution of various antioxidant enzymes.[65]

Ocimum sanctum
Ocimum sanctum commonly known as 'Holy Basil' belongs to the family Labiatae, is widely known for its various therapeutic effects. The possible role by which it brings relief in NP is by decreasing the oxidative stress and calcium levels, which have been known to play significant role in pathogenesis and perception of NP.[66]

Cannabis
Cannabis sativa contain a complex mixture of natural cannabinoids and other chemical compounds. The main psychoactive ingredient

of cannabis extract is D9tetrahydrocannabinol (THC). This is an agonist at the CB1 receptor, which is found at many sites within the central nervous system. Like the opioids, the cannabinoids modulate pain processing at multiple sites within the central nervous system.[67] Cannabinoids produce analgesia independently of opiates. Cannabinoid analgesia is well established in animal models of neuropathic pain but further studies on human subjects are required to demonstrate its efficacy.[68]

Capciasin

Capsaicin, the compound in chilli peppers that makes them taste hot. Topical creams with capsaicin are used to treat pain from postherpetic neuralgia and diabetic neuropathy (0.075% cream 3-4 times daily for eight weeks), osteoarthritis (0.025% cream four times daily), and rheumatoid arthritis. Capsaicin has also been used to treat pain due to pruritus, psoriasis, mastectomy, bladder disorders, and cluster headaches.[69]

Curcumma longa

Curcumin is a polyphenol found in the dietary spice turmeric (Curcuma longa Linn.). It is extracted from dried rhizomes of the perennial herb, which is a member of the ginger family. Curcumin has been demonstrated to have a variety of biologic activities, including anti-inflammatory activities and anticancer properities. Curcumin is known to exert its action through inhibition of mitogen-activated protein kinases.[70]

3) Devices

Neurostimulation therapy is increasingly being used to treat chronic neuropathic pain that is refractory to drug treatment. The neurostimulation techniques can be divided into noninvasive and invasive methods. The techniques discussed in this paper include the following: spinal cord stimulation, deep brain stimulation, peripheral nerve stimulation, percutaneous electrical nerve stimulation, percutaneous neuromodulation therapy, electroalgesia, transcutaneous electrical nerve stimulation, transcutaneous acupoint electrical stimulation, interferential current therapy, piezo-electric current therapy and H wave therapy.[71]

Spinal cord stimulation (SCS)

Spinal cord stimulation technique is used occasionally to ease the symptoms of neuropathic pain. The analgesic effects of spinal cord stimulation lasts for many hours after the stimulation has been stopped. The long lasting pain relief is thought to result from modulation of neurotransmitter system at the dorsal horn.[72] In this technique a lead is placed in the dorsal epidural space and connected with a subcutaneously implantable pulse generator (IPG). The cathode is situated between the area of dorsal median sulcus and the dorsal root entry zone. Upon stimulation current flows from cathode to anode. However, current flow chooses the path of lowest resistance and high electrical conductivity. Cerebrospinal fluid (CSF) obviously has the lowest electrical resistivity which is followed by longitudinal white matter. CSF is responsible for conducting approximately 90% of the applied current.[73]

Deep brain stimulation (DBS)

The foremost effort to treat pain using DBS[74] lead to the discovery of the gate control theory of pain transmission and the development of SCS.[75, 76] Various deep brain structures that were targeted for inducing analgesia include sensory thalamus, posterior limb of the internal capsule, and the periventricular / gray matter. The possible mechanism by which DBS alleviate pain is perhaps dependent on the position of the stimulating electrode.[77-79]

Peripheral nerve stimulation (PNS)

The first use of PNS for alleviating refractory pain was reported over 30 yr ago by Wall and Sweet.[80] Up till now, due to high success rate of PNS it has been most widely accepted for treatment of neuropathic pain (e.g., posttraumatic neuropathy, diabetic neuropathy) when the nerve lesion is distal to the site of stimulation.[81] The various advantages of peripheral nerve stimulation include easy surgical process, non-destructive and reversible when the patient turns the stimulator off.[82]

Percutaneous electrical nerve stimulation (PENS)

PENS was indicated for the treatment of intractable pain associated with chronic low back pain syndrome, cancer, and other disorders causing persistent pain. Electrical stimulation of the spinal cord was carried out by percutaneous insertion of electrodes into the epidural space. Theoretically PENS is associated to both electroacupuncture (which involves electrical stimulation of percutaneously placed needle probes) and transcutaneous electrical nerve stimulation (via cutaneous electrodes). PENS has the advantage of avoiding the resistance offered by the skin and efficiently delivers the electrical stimulus near to the peripheral nerve endings

positioned in the soft tissue ,muscle and in the affected region.[83-88]

Transcutaneous electrical nerve stimulation (TENS) and its various variants

In TENS there is transmission of electrical energy from an external stimulator to the peripheral nervous system through cutaneously placed conductive gel pads. TENS can be subclassified as :

a. low-intensity(1–2 mA), high-frequency (50–100 Hz) TENS
b. acupuncture-like high-intensity (15–20 mA), lowfrequency (1–5 Hz).[89]

Transcutaneous Acupoint Electrica Stimulation (TAES)

TAES is a variant of TENS therapy that involves applying cutaneous electrodes at classical Chinese acupoints and stimulating with alternating high- and low-frequency electrical current ("dense-disperse").[90]

Interferential Current Therapy (ICT)

Interferential Current Therapy (ICT) is another variant of TENS that uses the principle of amplitude modulation to decrease the discomfort of stimulating deeper tissues (e.g., muscle) when using transcutaneously applied electrical current. A combination of different stimulation frequencies are used (i.e., one fixed at 4 kHz and another within a variable range) to generate.[91] frequencies between 4 and 250 Hz which are alleged to more effectively penetrate the soft tissues while producing less discomfort at the skin surface.[92]

H-Wave Therapy (HWT)

HWT is also a type of electrical stimulation technique that causes direct, localized effect upon the conduction of peripheral nerves.[93] This technique was first used as a substitute to TENS for producing dental analgesia. Currently, it is indicated in the treatment of acute musculoskeletal injuries, postoperative pain, and also as a noninvasive form for producing local analgesia. Julka et al reported that transcutaneous H-wave therapy was found efficient in relieving symptoms in 76% of diabetic patients suffering with peripheral neuropathic pain.[94]

Piezo-Electric Current Therapy (PECT)

PECT is currently an exploratory analgesic technique. PECT device produces a burst of 10 electrical pulses (five positive and five negative), each lasting 2–3 ms. Each electrical burst produced lasts for 50 to 250 ms (depending on the motor speed set) and generates a current of approximately 25 mA. PECT application into skin produces a tolerable "pricking" pain sensation associated with a neurogenic inflammatory response which generally lasts for 3–4 h.[95]

Motor cortex stimulation

In past few years MCS has evolved as a potential tool for the treatment of drug resistant neuropathic pain. This technique requires implantation of epidural electrodes over the motor strip. Electrodes are most commonly set up through a frontoparietal craniotomy or burr hole in the central area, carried out under general anaesthesia. This procedure is non-invasive and found effective in relieving trigeminal neuralgia although it can be used for any drug resistant or chronic neuropathic pain.[96,97]

CONCLUSION

Disease or injury to peripheral or central nerves leads to release of various inflammatory mediators and modulation of ion channels all this collectively causes persistent neuropathic pain. The relief from pharmacological treatment in neuropathic pain is often insufficient and associated with multiple side effects, this lead to search for electrical neurostimulation devices. The stimulation techniques range from non-invasive procedures such as TENS, TAES to slightly invasive technique like PENS/PNT, and also include extremely invasive techniques such as DBS, SCS. A more profound study of the effect of various electrical stimulation patterns on the pain effect could lead to additional benefits with electrical neurostimulation therapies. Clinically drugs remain the mainstay in treatment of neuropathic pain and electroanalgesia is used only for treating drug resistant pain. Before initiating electrical neurostimulation the risk and benefits associated to it should be closely evaluated.

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